



DEPARTMENT OF THE NAVY
BUREAU OF MEDICINE AND SURGERY
2300 E STREET NW
WASHINGTON DC 20372-5300

IN REPLY REFER TO

BUMEDINST 6710.69
BUMED-05B1
26 Nov 97

BUMED INSTRUCTION 6710.69

From: Chief, Bureau of Medicine and Surgery
To: Stations Having Medical Department Personnel

Subj: USE OF INVESTIGATIONAL AGENTS IN HUMANS

Ref: (a) 21 CFR 56 (NOTAL)
(b) 32 CFR 219 (NOTAL)
(c) 45 CFR 46 (NOTAL)
(d) 21 CFR 312 (NOTAL)
(e) DoD Directive 3216.2 of 7 Jan 83
(f) SECNAVINST 3900.39B
(g) BUMED ltr 3900 ser 05A/97-1238 of 15 Jul 97 (NOTAL)
(h) Memorandum of Understanding (MOU) between the Federal Drug Administration (FDA) and the Department of Defense (DoD) on the Investigational Use of Drugs, Antibiotics, Biologicals, and Medical Devices by DoD of 21 May 87
(i) E.O. 12975 of 3 Oct 95

Encl: (1) NAVMED 6710/9, Investigational Agent Status Report

1. Purpose. To disestablish the Naval Investigational Drug Review Board (NIDRB) and publish revised policies and procedures for the use of investigational drugs, devices, and biologicals on human subjects involved in clinical or other research conducted by the Department of the Navy.

2. Cancellation. NAVMEDCOMINST 6710.4.

3. Definitions

a. Clinical Investigation. Any experiment that involves an investigational agent and one or more human subjects that either must meet the requirements for prior submission to the FDA under the Federal Food, Drug, and Cosmetics Act or the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

b. Emergency Use. The use of an investigational agent on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain full Institutional Review Board (IRB) approval. Any subsequent use of the investigational agent at the same institution is subject to IRB review.

c. FDA. Food and Drug Administration of the U.S. Department of Health and Human Services.

d. IDCI. Information Data for Clinical Investigators, prepared by and obtained from the sponsor of the investigational agent.

e. IRB. An Institutional Review Board is a locally constituted and convened board, established by references (a), (b), and (c), that has primary responsibility for the review of investigational protocols involving human subjects. Comprehensive review may be performed by a single board, or a protocol's scientific merit and design may be considered by a Scientific Review Committee and a Committee for the Protection of Human Subjects (CPHS) may be used to evaluate protocol safeguards for the rights and welfare of human subjects, and to determine the acceptability of the proposed study in terms of applicable laws and regulations, standards of professional conduct and practice, moral and ethical standards, and community attitudes. IRB approval of research may be subject to further appropriate review or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

f. Investigational Agent. An investigational biological, device, drug, color additive, or electronic product intended for human use or consumption.

g. Investigational Biological. A new biologic product, i.e., virus, therapeutic serum, toxin, antitoxin, or analogous product used in the prevention, treatment, or cure of disease or injury that is subject to license by the FDA.

h. Investigational Device. A device used in an investigational study involving human subjects, where the study is intended to determine if the device is safe or effective.

i. Investigational Drug

(1) A new drug not yet approved by the FDA for general marketing and human use, intended solely for investigational use by experts qualified by training and experience to investigate the safety and effectiveness of drugs. This category of drugs is exempt from the prohibition against introduction (or delivery for introduction) into interstate commerce for use in humans on the basis of Form FDA 1571, Investigational New Drug Application (IND), filed with the FDA.

(2) A drug, approved by the FDA for use as outlined on the package insert of the drug, whose proposed indication, dose, or route of administration differs significantly from that recommended.

(3) An unapproved combination of drugs, regardless of whether or not each component drug is FDA approved for the intended use of the combination.

(4) A biologic product that is used in vitro for diagnostic purposes.

j. Investigator. A physician, dentist, or clinical pharmacologist designated by the sponsor as qualified to perform a particular phase of an investigation and under whose immediate direction the investigational agent is administered or dispensed to a subject. Investigators must complete, for the sponsor, the Statement of Investigator (Form FDA 1572).

k. Minimal Risk. The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered by the research subjects in their daily life or during the performance of routine physical or psychological examinations or tests.

l. Satellite Medical Treatment Facility (MTF). Navy medical and dental treatment facilities that have not received Naval School of Health Sciences, Bethesda (NSHS) local approval authority for most clinical research.

m. Sponsor. The person or agency who assumes responsibility for compliance with the Federal Food, Drug, and Cosmetic Act and other pertinent Federal directives that regulate studies of investigational agents. The sponsor may be a manufacturer, scientific institution, military medical command, or a civilian investigator regularly and lawfully engaged in the investigation of new agents. The sponsor of an investigational drug or biological must obtain an IND number by submitting FDA 1571 to the FDA. The sponsor of an investigational device must obtain an FDA investigational device exemption (IDE) number before proceeding with a study. When the Navy assumes sponsorship of an investigational agent, the sponsor must be a field activity under the Chief, Bureau of Medicine and Surgery which is qualified to undertake the responsibilities of sponsorship.

n. Study Phases of FDA Regulated Clinical Investigations. The phase of a particular study is determined by the FDA after consideration of supporting data supplied by the sponsor. Following the completion of preclinical studies on experimental animals, protocols testing investigational new drugs and biologics in humans progress through three phases, defined by reference (d):

(1) Phase 1. Tests are performed to determine toxicity, metabolism, absorption, elimination, other pharmacological actions, preferred route of administration and safe dose range.

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The investigator must be able to evaluate the toxicity and pharmacological effect of the drug or biological on humans. The sponsor must approve, monitor, and collate all Phase 1 data. To ensure each investigator is qualified and that the facilities are adequate, the sponsor must obtain an FDA 1572 from each investigator.

(2) Phase 2. Initial trials are conducted on a limited number of patients for treatment or prevention of a specific disease to determine safety and efficacy. The investigator should be a physician, dentist, or clinical pharmacologist familiar with the conditions to be treated, the agents used in these conditions, and the methods of their evaluation. The responsibilities and reporting requirements of the sponsor and each investigator are the same as for Phase 1 studies.

(3) Phase 3. Clinical trials are designed to assess the safety, effectiveness, and optimum dosage in treating a specific disease in a large group of subjects. This phase is normally conducted by separate groups following the same scientific protocol to produce well-controlled data. In addition to experienced investigators, clinicians not regarded as specialists in clinical pharmacology may serve as investigators. To ensure each investigator is qualified and the protocol and the facilities are adequate, the sponsor must obtain an FDA 1572 from each investigator. The sponsor will, in turn, submit copies of these forms and other materials to the FDA as part of the total study document package.

o. Supporting MTF. A Navy MTF that has received NSHS Bethesda local approval authority for most clinical research.

4. Background. Reference (e) authorizes Service Secretaries to delegate approval authority for DoD supported human subjects research to the "lowest level operating a human-subjects review process" in the military chain of command. Reference (f) delegates Secretary of the Navy approval authority to the Navy Surgeon General for all human subjects studies within his or her purview except those specifically requiring Assistant Secretary of the Navy (Research, Engineering and Systems (ASN(RE&S))), now ASN (Research, Development and Acquisition (RD&A)) approval, and the Surgeon General "may further delegate this approval authority as appropriate." By reference (h), the Surgeon General delegated his approval authority to the Commanding Officer (CO), NSHS Bethesda. Although reference (f) specifies the role of the NIDRB, the establishment of an NIDRB was a consequence of a pre-existing MOU between the FDA and the DoD. That MOU was updated in 1987 as reference (h) and gives the DoD Surgeons General the option either to use central review panels and retain headquarters approval authority for research using investigational agents, or to delegate such review and approval authority to medical department components.

5. Policy

a. Except for special categories of research that require higher level approval per reference (f), approval authority for human subjects research using investigational agents as part of research, development, test and engineering (RDT&E) studies, Program 6 is delegated to the Director, Research and Development (MED-26) and may be delegated further.

b. Except for special categories of research that require higher level approval per reference (f), and for studies involving retroviruses, or use of nonhuman primates, dogs, cats, or marine mammals, approval authority for human subjects research using investigational agents as part of clinical investigation studies, Program 8 is delegated to the commanders of supporting MTFs.

c. Commanders of satellite MTFs are authorized and encouraged to participate in clinical research using investigational agents, provided that protocols originating at their facility are favorably endorsed by the IRB (or CPHS) at their supporting MTF.

d. All human subjects research using investigational agents shall be considered to be greater than minimal risk.

e. Emergency use procedures are intended for one-time use for one subject patient at any given MTF. They must not be used again for the same protocol to evade routine review and approval procedures when future use of the agent is anticipated at the MTF.

6. Responsibilities

a. Director, Research and Development (MED-26). MED-26 will ensure compliance with this instruction and all pertinent directives governing human subjects research using investigational agents, and supported by RDT&E Program 6 appropriated funds. MED-26 will provide further procedural guidance as necessary.

b. CO, NSHS Bethesda. Ensures the annual inspection for recertification of supporting MTFs specifically examines the special review, management, and administration requirements for clinical protocols involving investigational agents.

c. COs of Supporting MTFs Officers will:

(1) Ensure compliance with this instruction and all pertinent directives governing clinical research with investigational agents.

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(2) Provide around-the-clock access to the chair of their IRB or CPHS to enable timely consideration of local and of satellite MTF emergency use requests.

(3) Provide a complete copy of all correspondence with the FDA pertaining to clinical studies with investigational agents to the CO, NSHS Bethesda (Code OC) within 5 working days of receipt or transmission.

d. COs of Satellite MTFs. Even though research protocols from their activity are required to be reviewed and approved at sites away from their facility, commanders are responsible for all research conducted at their command. COs will:

(1) Ensure compliance with this instruction and all pertinent directives governing clinical research with investigational agents. All personnel who are involved in research must be adequately trained and competent to perform their research-related duties.

(2) Provide for local review of all clinical investigation protocols using investigational agents. If favorably endorsed, protocol packages will be forwarded to the supporting MTF's clinical investigation department (CID) for additional review and consideration for approval. Research may begin when written notification of approval is received from the approving authority.

(3) Provide around-the-clock access to a senior pharmacy officer or staff pharmacist to enable timely review of local emergency use requests.

(4) Provide a complete copy of all correspondence with the FDA pertaining to clinical studies with investigational agents to the CO, NSHS Bethesda (Code OC) within 5 working days of receipt or transmission.

7. Routine Procedures

a. Non-Navy Sponsored Agents. Most protocols for clinical trials of investigational agents submitted by Navy investigators will be sponsored by an organization other than the Navy. The following information is required as an appendix to the documents commonly prepared for greater than minimal risk human subjects research protocols. The entire package shall be routed locally for endorsements and submitted to the cognizant IRB for review and processing.

(1) The IDCI, FDA-approved, IDE application or other official, sponsor-provided, investigational agent data package. The format and content of this package will differ, depending upon whether the agent is a drug, biological, or device.

(2) A statement signed by the principal investigator (PI) and all associate investigators certifying that they have read and understood the sponsor's data package.

(3) The name of the manufacturer and supplier of the agent, if different from the sponsor.

(4) A description of the sponsor's program, and the role of local Navy participation in the program.

(5) Any information pertinent to the safety and therapeutic use of the agent in addition to the IDCI, IDE, or other sponsor-provided data package.

(6) A statement that written informed consent will be obtained from all subjects. If an exception to consent is requested, a detailed justification for waiver of consent is required.

(7) A copy of the completed FDA 1572 or other investigator signature form, as determined by the sponsor.

b. Navy-Sponsored Agents. A Navy physician may want to investigate an agent not yet approved by the FDA and not sponsored by another organization for clinical testing. Multiple parts of Title 21, Code of Federal Regulations specify the various formats and content for sponsor's document packages required by the FDA, depending on the specific category of investigational agent. That information is required as an appendix to the documents commonly prepared for greater than minimal risk human subjects research protocols. The entire package shall be routed locally for endorsements, and submitted to the appropriate IRB for review and processing. In all cases, the CO's signature from the requesting command (the intended performance site of the investigation) must be on the appropriate documents (e.g., FDA 1571) before submitting to the FDA or forwarding to the supporting MTF. Studies may begin after the CO has been notified in writing by the FDA of the IND number or IDE number assigned to the protocol.

8. Emergency Procedures. Urgent situations may arise when the use of an investigational agent is indicated if a patient's life is threatened, there is no comparable or satisfactory alternative therapy, there is no relevant, locally approved study for the investigational agent, and it is impractical to convene an IRB on short notice. Reference (a) exempts the FDA's requirement for prior IRB approval before using an investigational agent at a specific institution in the case of, "emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review." Emergency requirements do not relieve the Navy clinician from

FDA requirements for the use of investigational drugs. The clinician must be a designated PI or an associate investigator on an approved investigator's FDA 1572. Permission to waive informed consent will require favorable endorsement by the MTF CO and chair of the MTF's IRB or CPHS (in the case of requests at supporting MTFs) or by the local MTF CO and chair of the supporting MTFs IRB or CPHS (in the case of requests at satellite MTFs).

a. Data package. In emergency circumstances, the following information must be assembled, with items (1) through (7) specified on a cover page:

- (1) Requesting activity's name and request date.
- (2) Name of investigational agent and supplier.
- (3) Sponsor's name, address, telephone number, and IND or IDE number. (If a Navy activity is the sponsor, an FDA 1571 must be completed, signed by the local MTF commander, and added to the data package.)
- (4) Phase of the investigation (obtained from sponsor).
- (5) PI's name, degree, department, office telephone number, and preferably telefax number, pager number, and e-mail address.
- (6) Patient's name, age, military sponsor's social security number, beneficiary status, and diagnosis.
- (7) Clinical reason (indication) for the request.
- (8) Complete copy of the investigational protocol.
- (9) IDCII or equivalent for the investigational agent.
- (10) Copy of completed FDA 1572.
- (11) Curriculum vitae for the PI.
- (12) Copy of the patient consent form or detailed explanation of why consent should be waived.

b. Supporting MTFs. The data package and cover page will be prepared with dated signature spaces for the PI, chair IRB (or CPHS), and the MTF commander.

(1) During Normal Duty Hours

(a) The PI will submit the completed data package to CID. The CID will check the package for completeness and route it on a priority basis to the other signatories for review and

signature. The CID will coordinate communications among the parties if any of the reviewers have concerns, questions, or require clarification from the PI, and will notify the PI after all cover-page signatures have been obtained.

(b) The PI executes the consent process for the intended patient, and if signed consent is obtained, requests the sponsor to ship the investigational agent to the pharmacy. The PI proceeds with the protocol.

(2) After Normal Duty Hours. These procedures are intended for use only in immediate, critical, medical emergencies where delay until normal duty hours is medically inappropriate.

(a) The PI contacts the chair IRB (or CPHS) and the CO by using procedures directed by local policy. Although not mandatory, it is strongly recommended that the chair IRB (or CPHS) review the cover page, and items (10) and (12) from the data package before approving the protocol. Initial approval can be documented by signatures in ink, by telefax, or the PI may be authorized to annotate the signature space indicating the time and date verbal approval was granted by telephone. In all cases of verbal or telefax approval, actual signatures must be obtained on the original cover page and the complete data package provided to the chair IRB (or CPHS) within 5 working days.

(b) If approval is granted, the PI executes the consent process for the subject patient, and if signed consent is obtained, requests the sponsor to ship the investigational agent to the pharmacy. The PI proceeds with the protocol.

c. Satellite MTFs. The data package and cover page will be prepared with dated signature spaces for the PI, local senior pharmacy officer or staff pharmacist, the local MTF commander, and the chair IRB (or CPHS) of the supporting MTF. All completed, approved, emergency use protocol packages, with authenticating signatures verifying any telephone approval annotations on the cover page, must be mailed to the chair IRB (or CPHS) of the supporting MTF within 5 working days of approval using an accelerated delivery process.

(1) During Normal Duty Hours

(a) The PI will obtain the local approval signatures on the cover page, using procedures directed by local policy.

(b) The PI will contact the chair IRB (or CPHS) at the supporting MTF to obtain approval. Initial approval can be documented by telefax, or the PI may be authorized to annotate the signature space on the cover page to indicate the time and date verbal approval was granted by telephone. Although not

mandatory, it is strongly recommended that the chair IRB (or CPHS) review a telefax transmission of the locally signed cover page, and items (10) and (12) from the data package before approving the protocol.

(c) The PI executes the consent process for the subject patient, and if signed consent is obtained, requests the sponsor to ship the investigational agent to the pharmacy. The PI proceeds with the protocol.

(2) After Normal Duty Hours. These procedures are intended for use only in immediate, critical, medical emergencies where delay until normal duty hours is medically inappropriate.

(a) The PI will obtain all required local approval signatures, using procedures directed by local policy. Initial approval can be documented by signatures in ink, by telefax, or the PI may be authorized to annotate the signature space to indicate the time and date verbal approval was granted by telephone. In all cases of telephone or telefax approval, actual signatures must be obtained on the cover page to verify telephone or telefax annotations.

(b) The PI will contact the chair IRB (or CPHS) at the supporting MTF to obtain approval, as described above in 8c(1)(b).

(c) If approval is granted, the PI executes the consent process for the subject patient, and if signed consent is obtained, requests the sponsor to ship the investigational agent to the pharmacy. The PI proceeds with the protocol.

d. Distribution of Documents

(1) The PI keeps the original signed consent form, and ensures a copy of the signed consent and the privacy act statement is filed in the subject's health record, together with sufficient documentation to clearly identify by name or code the investigational agent. Significant observations and any adverse effects must also be recorded in the health record.

(2) The patient receives a copy of the signed consent form.

(3) The pharmacy receives a copy of the entire protocol package, including signed cover page and signed consent form.

(4) The cognizant CID receives the original signed cover page, original protocol and supporting documents, along with a copy of the signed consent form within 5 working days. A complete copy of the entire protocol package is forwarded by the CID to the CO, NSHS Bethesda, (Code OC).

9. Naval Personnel or Facilities on Foreign Soil

a. Naval personnel stationed on foreign soil must comply with this instruction when using investigational agents with any patient in a facility under the administrative control of the U.S. Government. This applies to:

- (1) Investigational agents having a U.S. sponsor.
- (2) Foreign investigational agents without U.S. status.

b. If a patient using an investigational agent is transferred to another MTF, the PI will notify the chair IRB (or CPHS) of the supporting MTF with cognizance of that investigation as soon as possible before the transfer to determine feasibility of continuing the protocol at the receiving MTF. Notification must include the name of the agent, condition for which it is being used, and the name and destination of the patient.

c. The use of investigational agents involving non-U.S. citizens at overseas activities must be approved by the CO and must comply with the legal requirements of the host country. This requirement applies whether the study is conducted at the overseas U.S. naval facility or whether a U.S. Navy physician or dentist is participating in a joint study with local investigators at another facility within the host country.

10. Classified Agents. The general policy of the Department of the Navy is not to classify medical research. However, should it become necessary to classify for reasons of national security the testing of a drug, biological, or medical device that would normally fall under the provisions of Title 21 of the Code of Federal Regulations, these studies will be handled under the special provisions of reference (h). Per reference (i), there will be distinct clarification of the protection for human subjects in all classified research within DoD.

a. For clinical investigations with Navy-developed agents that are classified for reasons of national security, NSHS Bethesda, Code OC will provide guidance and coordination.

b. For RDT&E studies with Navy-developed agents that are classified for reasons of national security, MED-26 will provide guidance and coordination.

11. Local Handling of Investigational Agents

a. The investigational agent will be requisitioned from the manufacturer, sponsor, or other source, specifying the shipment be made directly to the pharmacy.

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b. Upon receipt, the pharmacy officer will prepare appropriate documents to add the agent to inventory, clearly identifying it as an investigational agent.

c. The pharmacy will attach to each container a distinctive label containing the statement, "Investigational Drug - Not for General Use," the name of the drug (or if a code number is used, the pharmacological classification, e.g., antihistamine, analgesic, etc.), and the name of the PI.

d. The pharmacy will designate a locked area for the storage of investigational agents. Ideally, this area should be exclusively for the storage of investigational agents.

e. The PI or authorized associate investigators (as indicated on the FDA 1572) will request the agent from the pharmacy by means of a written prescription form. The pharmacy will not honor any prescription signed by a person other than the designated investigators. Electronic prescription systems (e.g., CHCS) may be used provided durable hard copy printouts can be generated for the pharmacy's investigational agent file and provided the electronic prescription system is sufficiently secure to be used to prescribe Drug Enforcement Agency schedule II controlled drugs.

f. The prescription will be kept in a separate file, numbered consecutively, and the number prefixed by "IND."

g. A separate investigational drug inventory and prescription record will be maintained in the pharmacy for each investigational agent. This will provide a perpetual pharmacy inventory and serve as a ready reference for all patients receiving the agent.

h. When the agent is delivered to the ward or clinic, it will be accompanied by the same system of records used for controlled drugs to document transfer and custody. A receipt will be obtained and returned to the pharmacy. Nursing personnel are responsible for returning unused agents to the pharmacy along with appropriate documents.

i. The PI is directly responsible for all use of investigational agents.

j. Nurses may administer investigational agents only under the supervision of a PI or associate investigators who have been identified in writing in the protocol package as qualified to administer or supervise the administration of the investigational agent. Nurses who administer investigational agents must be specifically designated by the PI and must be provided with such basic information as the name of the agent, preparations, dosage forms, strengths available, actions and uses, side effects, and symptoms of toxicity.

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k. The pharmacy will dispose of (by return to the manufacturer or by destruction, as indicated) all agents no longer in use or for which future use is not anticipated.

1. If "double-blind" studies or any other studies requiring coding are used, a copy of the code will be in the pharmacy.

12. Reports and Form

a. Reports. Annually, and within 10 days of the conclusion of the study at a Navy activity, a report must be prepared by the PI describing the results and including a case summary. All data fields and data elements of enclosure (1) must be addressed. However, the use of NAVMED 6710/9, Investigational Drug Status Report is optional. A copy of the report shall be retained permanently in the cognizant IRB or CPHS protocol file.

(1) Reports of studies under the cognizance of MED-26 will be addressed to MED-26, via the CO of the performing activity.

(2) Reports of studies under the cognizance of NSHS Bethesda (Code OC) will be addressed to NSHS Bethesda (Code OC) via the CO of the performing activity. If the performing activity is a satellite MTF, the CO of the supporting MTF will be interposed in the reporting chain.

b. Forms

(1) NAVMED 6710/9 (9-97) is provided in enclosure (1) and is authorized for local reproduction.

(2) FDA 1571 (1-97), Investigational New Drug Application (IND) and FDA 1572 (1-97), Statement of Investigator are available from the Food and Drug Administration at the following internet address: <http://aosweb.psc.dhhs.gov/forms/fdaforms.htm> or by telefax on demand at 1-800-342-2722.



W. H. SNELL
Assistant Chief for
Education, Training,
and Personnel

Available at:
<http://support1.med.navy.mil/bumed/instruct/external/external.htm>

INVESTIGATIONAL AGENT STATUS REPORT	REPORT SYMBOL MED 6710-10
1. FROM: TO: VIA:	
2. CIP/R&D PROJECT NO.	
3. TITLE	
4. INVESTIGATIONAL AGENT	
5. REPORT TYPE <div style="display: flex; justify-content: space-between;"> First report? <input type="checkbox"/> Yes <input type="checkbox"/> No </div> <div style="display: flex; justify-content: space-between;"> Second report? <input type="checkbox"/> Yes <input type="checkbox"/> No </div> <div style="display: flex; justify-content: space-between;"> Adverse event report? <input type="checkbox"/> Yes <input type="checkbox"/> No </div>	
6. PROJECT STATUS <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> Column A <input type="checkbox"/> Emergency Use-one patient only <input type="checkbox"/> Ongoing approved protocol <input type="checkbox"/> Drug has received FDA approval (Date of FDA approval _____) </div> <div style="width: 30%;"> Column B <input type="checkbox"/> Drug or device used <input type="checkbox"/> Drug or device not used </div> <div style="width: 30%;"> Column C <input type="checkbox"/> Protocol active <input type="checkbox"/> Protocol completed <input type="checkbox"/> Protocol abandoned </div> </div>	
7. PRIMARY EFFECT <input type="checkbox"/> No effect <input type="checkbox"/> Positive effect on the course of patient's condition <input type="checkbox"/> Undetermined effect <input type="checkbox"/> Adverse effect (<i>Unusual in severity, timing, etc., or unanticipated, such as not listed in the informed consent. Specify below.</i>)	

8. SIDE EFFECTS

☐ None noted ☐ Unlikely ☐ Possible

☐ Probable relation to investigational agent

☐ All side effects were explained within the consent form

☐ Side effects were unanticipated and not explained with the informed consent. *(Specify below, attach a copy of the revised CPHS-approved consent form which indicates the new side effects, and complete section 9.)*

9. REPORT OF ADVERSE PRIMARY SIDE EFFECTS

☐ No adverse events

a. Date adverse effects were reported to:

CPHS _____

Drug Sponsor _____

FDA _____

NSHS _____

b. Adverse effects occurred, but were not reported. *(Explain why they were not reported.)*

10. DATE OF MOST RECENT PROTOCOL REVIEW BY THE CPHS

11. SIGNATURE AND GRADE OF PRINCIPAL INVESTIGATOR

DATE